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| 09/891,517 | 06/27/2001 | Ryuichiro Kurane | 210352US0X | 8807 |

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EXAMINER

CLOW, LORI A

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| ART UNIT | PAPER NUMBER |
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1631

DATE MAILED: 02/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/891,517

Applicant(s)

KURANE ET AL.

Examiner

Lori A. Clow, Ph.D.

Art Unit

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 09 September 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 82-108 is/are pending in the application.
- 4a) Of the above claim(s) 87-94 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 82-86 and 95-108 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 27 June 2001 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114.

Applicants' response, filed 9 September 2005, has been fully considered. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Claims 82-108 are currently pending. Claims 1-81 have been cancelled. Claims 82-86 and 95-108 are hereby examined, as they are drawn to the elected invention.

Applicants state that claims 87-94 depend from claim 82, and therefore, should be examined. This is not persuasive. As was noted in the Previous Office Action, newly submitted claims 87-94 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons:

Claims 87 and 88 correspond to original claim 44, which was previously restricted to Group XII, drawn to an eighth method, PCR-based.

Claim 89 corresponds to original claim 46, which was restricted to Group XIV, drawn to a tenth method, PCR-based (qtPCT).

Claims 90-94 correspond to original claims 51 and 52, which were restricted to Group XV, drawn to a data analysis method.

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Since Applicants have received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 87-94 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 9 October 2003.

Priority

Foreign priority to Japanese Applications 193133/2000 (June 27, 2000), 236115/2000 (August 3, 2000), and 292483/2000 (September 26, 2000) is hereby acknowledged. All copies of foreign priority documents have been received.

Sequence Listing

It is noted that this Application is now in sequence compliance and the Sequence Listing has been entered (6/28/05).

Drawings

The drawings submitted 27 June 2001 are accepted. It is noted that the Specification has been corrected to include SEQ ID NOs. in the Brief Description of the Drawings.

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Specification

The use of the trademark FluoReporter Kit has been noted in this application, for example (page 117). It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

It is noted that there may be other instances of trademarks in the specification and that this is merely **an example**.

The corrections to the Specification submitted 9 September 2005 have been entered.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 82-86 and 95-108 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 82 (and dependent claims) recite, in the preamble, “a quantitative polymorphous analysis method”. It is unclear, from the final step, whether an actual analysis has occurred. There is no final step of quantitating polymorphisms of the target gene. Rather, the final step is drawn to determining the initial amounts of the individual species of the target gene. It is

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unclear, in the claim language, how the initial concentration and the species concentration relate to one another to quantitate polymorphisms. Clarification is requested.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 82, 84-86, and 96 are rejected under 35 U.S.C. 102(e) as being anticipated by US 6,699,661 B1 (Kurane et al.)

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention “by another,” or by an appropriate showing under 37 CFR 1.131.

In regard to claim 82, Kurane teaches a method for determining a concentration of a target nucleic acid by using nucleic acid probe labeled with a fluorescent dye (see abstract), wherein:

a) a target gene is amplified and monitored by real-time PCR (step d. at column 5, lines 5-7; column 18, lines 17)

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b) polymorphism analysis (column 8, lines 53-54; column 12, lines 20-52)

c) determining target amount (column 8, lines 59-61)

d) determining species amount (column 9, lines 30-35).

In regard to claim 84, Kurane teaches that the probe is end labeled with a fluorescent dye (column 9, lines 43-50). The probe hybridizes at the end portion of the target where at least one G (guanine) base exists in a base sequence of the target at a position 1 to 3 bases apart from an end base of the target (column 11, lines 14-18; column 19, lines 2-11). Further, the fluorescent dye is reduced in fluorescence emission when the probe hybridizes to the target (column 15, lines 61-64).

In regard to claim 85, Kurane teaches the end labeled probe, as above, wherein the probe has a sequence designed such that when the probe hybridizes to the target, plural base pairs in a probe-nucleic acid complex form at least one G (guanine) and C (cytosine) pair (column 11, lines 19-21) and the fluorescence is reduced, as above.

In regard to claim 86, Kurane teaches a nucleic acid probe wherein the probe is labeled with a fluorescent dye and is modified on the 3' and 5' end (column 19, lines 12-32) and becomes one pair at the modification portion (column 19, lines 39-45).

In regard to claim 96, Kurane teaches a method wherein polymorphism analysis is determined using a sequencer (column 12, lines 48-51).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

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(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35

U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 83, 95, and 99-108 are rejected under 35 U.S.C. 103(a) as being obvious over US 6,699,661, as applied to claim 82 above, in view of US 6,727,356 B1 (Reed et al.).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of

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invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. 103(c) as prior art in a rejection under 35 U.S.C. 103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

In regard to claim 82 above, Kurane teaches a method for determining a concentration of a target nucleic acid by using nucleic acid probe labeled with a fluorescent dye (see abstract), wherein:

a) a target gene is amplified and monitored by real-time PCR (step d. at column 5, lines 5-7; column 18, lines 17)

b) polymorphism analysis (column 8, lines 53-54; column 12, lines 20-52)

c) determining target amount (column 8, lines 59-61)

d) determining species amount (column 9, lines 30-35).

In regard to claims 99 and 100, Kurane teaches that the probe is labeled on the 3' end or the 5' end, respectively, with fluorescence (column 19, lines 12-32).

In regard to claim 101, the probe has G or C as a 3' end base (column 19, lines 1-32).

In regard to claim 102, the probe has G or C as the 5' end base (column 19, lines 1-32).

In regard to claim 103, the hydroxyl group has been phosphorylated (column 11, lines 33-64).

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In regard to claim 104, the probe is labeled at 5' end or 3' end phosphate group (column 11, lines 33-64).

In regard to claim 105, the oligonucleotide probe is chemically modified (column 10, line 17).

In regard to claim 106, the modification is 2'-O-methyloligonucleotide (column 10, line 18).

In regard to claims 107 and 108, the probe comprises ribonucleotide and deoxyribonucleotide and the oligo comprises 2'-O-methyloligonucleotide (column 10, lines 17-22).

Kurane does not specifically teach that the probe is labeled with a fluorescent dye and **quencher** substance, wherein the intensity of the fluorescence in a hybridization reaction **increases** when the probe hybridizes with the target, as in claim 83.

However, Reed teaches fluorescent quenching detection reagents and methods (abstract). In particular, with regard to claim 83, Reed discloses a quencher for use in analytical methods, such a FRET analysis. IN FRET, fluorophores are attached at 5' and 3' positions, as in the instant invention (column 5, lines 4-16). The methods are directed to detection of PCR-generated nucleic acid sequences. One application of the method disclosed by Reed is one or more fluorescent oligonucleotide conjugates used as probes to identify a target nucleic acid by assaying hybridization between the probes and the target (column 36, lines 23-27). To do so, a probe containing both a fluorescent label and a quenching agent, which quenches the fluorescence emission of the fluorescent label is employed (column 37, lines 27-29), as in claim 83. Further, subsequent to hybridization of the fluorophore/quencher-labeled probe to its target,

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it becomes a substrate for the exonucleolytic activity of a polymerizing enzyme which has initiated polymerization at an upstream primer. Exonucleolytic degradation of the probe releases the fluorescent label from the probe, and hence from the vicinity of the quenching agent, allowing detection of a fluorescent signal (column 37, lines 35-42).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have incorporated the quencher probes of Keen into the method of Kurane, for the detection of polymorphisms. One would have been motivated to do so because Kurane teaches that the method of the invention is appropriate for measuring the change in the intensity of fluorescence corresponding to the concentration of target nucleic acid, and therefore the target may be quantitated from that change (column 14, lines 14-26). The quencher system of Keen was designed specifically to work with the 3' 5' FRET assay, as stated above.

Claim 95 is rejected under 35 U.S.C. 103(a) as being obvious over US 6,699,661 (Kurane), as applied to claim 82 above.

In regard to claim 95, Kurane does not specifically teach that the polymorphism analysis is a T-RFLP, RFLP, SSCP, or CFLP method. However, it would have been *prima facie* obvious to one of ordinary skill in the art at the time of the invention to have used a method, such as SSCP, in which melting curve analysis yields information regarding polymorphisms, in the method of Kurane. One would have been motivated to do so because Kurane, himself, uses melting curve analysis in the assay for polymorphisms (column 14, lines 36-44) in which SNPs are detected. One method of detecting SNPS, well known in the art, is SSCP analysis.

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Conclusion

The outstanding rejections under 35 USC 112, 1st paragraph for new matter have been withdrawn in view of Applicants amendments to the claims.

The outstanding rejections under 35 USC 112, 2nd paragraph, present in the previous Office Action, have been withdrawn in view of Applicant amendments to the claims.

No claims are allowed.

Inquiries

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The Central Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lori A. Clow, Ph.D., whose telephone number is (571) 272-0715. The examiner can normally be reached on Monday-Friday from 10 am to 6:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, Ph.D., can be reached on (571) 272-0718.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

February 6, 2006

Lori A. Clow, Ph.D.

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Lori A. Clow

Patent Examiner